

OPEN PEER REVIEW

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Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

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Peer Review Report for "Down-Regulation of *HOTAIR*, *SUZ12*, and *DNMT3A* by Curcumin Nanoparticles in Glioblastoma"

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Review Timeline:

Submit Date: 26 Oct 2024

Revised Date: 24 Jan 2025

Accepted Date: 22 Feb 2025

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Amanollah Zarei-Ahmady : Reviewer

30 Nov 2024

Dear Author,

Please find my comments and questions on "Curcumin nanoparticle has a potential inhibitory effect on glioblastoma cell line through down-regulation of epigenetic factors" manuscript as below.

- 1) Please change title of manuscript as below: Curcumin nanoparticle potential inhibitory on glioblastoma cell line through down-regulation of epigenetic factors
- 2) Why you select two method of nanoparticles preparation? "we used curcumin NPs produced through wet milling and ultrasonic methods." Which one was better? I didn't find the answer in abstract!
- 3) "A transmission electron microscope (Zeiss-EM10C-80 KV, Germany) was used to investigate the morphology and size of curcumin NPs" this part should transfer to first part of "material and methods".

4) "The results of the absorption spectrum measured with an ultraviolet-visible spectrometer were analyzed using Excel software. The highest NPs absorption was observed at the wavelength of 160 nm, and its value was equal to 0.51." Let me your conclusion clearly and the main purpose of UV analysis.

5) Update your refrencess.

I found this manuscript suitable for publish in JJNPP only after major revision.

Best Regards,

A.Z-A

Associate Professor of Organic Chemistry

Esmail Mohammadian : Reviewer

2 Dec 2024

Dear Editor

Have a nice day.

The author studied Curcumin nanoparticle has potential inhibitory effect on glioblastoma cell line through down-regulation of epigenetic factors.

I would suggest reconsidering the manuscript for publication only after the following major revision.

1. The title needs to be changed.
2. Please rewrite the abstract section completely (with SD values).
3. Please mention the novelty of the present research in the introduction section. Please rewrite the introduction section based on the title.
4. The manuscript is poorly written (result and conclusion sections).

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Answers to the referee's questions

Reviewer 1

Dear Referee

First of all, thank you for your valuable and important comments.

Your questions and comments are numbered and the answers are under each question.

1- The background is informative but repetitive in sections. For example, the role of curcumin in DNA methylation is described in multiple places. Streamline the content to avoid redundancy.

Answer: Thank you for your valuable suggestion. In various sections of the manuscript, efforts were made to eliminate redundant content to ensure clarity and conciseness. However, based on feedback from the reviewers, several adjustments and modifications have been implemented throughout the article to address their suggestions. These changes include refining the structure, enhancing the depth of analysis, and incorporating additional insights where necessary. Particular emphasis was placed on aligning the content with the reviewers' recommendations to improve the manuscript's overall quality and coherence. Furthermore, the updated sections aim to maintain a balance between brevity and comprehensiveness, ensuring that the key points are conveyed effectively while avoiding unnecessary details. These revisions reflect a careful consideration of the reviewers' input to make the manuscript more robust and better suited for its intended audience.

2- Statistical significance is mentioned (e.g., p-values), but the manuscript does not describe the statistical tests sufficiently. Adding a subsection explaining the rationale for using specific tests would improve clarity.

Answer: Thank you for your valuable suggestion. In the revised manuscript, references to statistical tests and p-values were included in the relevant sections to provide a robust foundation for the findings and their significance. Additionally, a dedicated section was added to elaborate on the statistical methods employed in the study. This new section outlines the rationale for selecting specific statistical approaches, describes the tests used for data analysis, and explains how p-values were calculated to assess the significance of the results.

3- Although the discussion interprets the results well, it over-relies the literature to explain observations without linking the findings back to the study's specific methodology.

Answer: Thank you for your constructive feedback. We have revised the discussion section to establish a direct connection between the study's methodology and the results. The methods used are now explicitly referenced to explain how they contributed to the observed findings. We have enriched the discussion by providing detailed interpretations that are directly grounded in the study's design and procedures, ensuring a more robust and study-specific narrative. These revisions have strengthened the discussion by better integrating the study's methodology with its findings, as recommended. We are grateful for the reviewer's valuable input, which has contributed to enhancing the clarity and scientific rigor of the manuscript.

4- Enhance figure captions by specifying the experimental context (e.g., concentration of curcumin used, the specific cell line tested).

Answer: Thank you for your constructive feedback. we have revised the figure captions to include detailed information such as the concentration of curcumin used, the specific cell line tested, and other relevant experimental conditions. Thank you for this valuable feedback, which has helped us to refine the presentation of our results.

Reviewer 2**Dear Referee**

First of all, thank you for your valuable and important comments.

Your questions and comments are numbered and the answers are under each question.

1- The title needs to be changed.

Answer: Thank you for your suggestion regarding the title. We have revised the title of the article as recommended to more accurately reflect the focus of the study on the inhibitory effects of curcumin nanoparticles on glioblastoma cells through the reduction of epigenetic factors, including HOTAIR, SUZ12, and DNMT3A.

2- Please rewrite the abstract section completely (with SD values).

Answer: Thank you for your suggestion regarding the abstract. This section has been completely rewritten and the requested SD values have been included to provide greater clarity and accuracy in presenting the results.

3- Please mention the novelty of the present research in the introduction section. Please rewrite the introduction section based on the title.

Answer: Thank you for your valuable suggestion. We have revised the Introduction section to clearly highlight the novelty of the present research. The section has been updated to focus on the potential inhibitory effects of curcumin nanoparticles on glioblastoma cells through downregulation of epigenetic factors, including HOTAIR, SUZ12, and DNMT3A, as indicated in the new title.

This study provides a comprehensive and detailed investigation of the effects of curcumin nanoparticles (NPs) on epigenetic regulation in glioblastoma (GBM) and advances our understanding of the role of this natural compound in cancer therapy. The use of ultrasonication to improve the physicochemical properties of curcumin, including increased water solubility, stability, and optimal particle size, is one of the key innovations of this study. Furthermore, the focus on the effects of curcumin nanoparticles on key genes such as DNMT3A, SUZ12, HOTAIR, and MecP2 represents an innovative and comprehensive approach.

This study is the first to directly evaluate the effect of curcumin on SUZ12 gene expression in glioblastoma, highlighting its role in inducing apoptosis and suppressing cell invasion. This study also examines the interaction of HOTAIR with the PRC2 complex and shows how curcumin nanoparticles can disrupt this interaction, providing new insights into the epigenetic regulation of cancer pathways. These findings identify curcumin as a promising agent for targeted and combination cancer therapies.

4- The manuscript is poorly written (result and conclusion sections).

Answer: Thank you for your constructive feedback. We sincerely appreciate your comments regarding the results and conclusion sections. We have carefully revised these sections to improve clarity, structure, and overall readability. We have also ensured that the interpretation of the results is more concise and directly linked to the key findings of the study. I hope the revised version addresses your concerns effectively.

Reviewer 3

Dear Referee

First of all, thank you for your valuable and important comments.

Your questions and comments are numbered and the answers are under each question.

1- Please change title of manuscript as below: Curcumin nanoparticle potential inhibitory on glioblastoma cell line through down-regulation of epigenetic factors

Answer: Thank you for the suggestion regarding the title. The requested revision has been made, and the title has been changed to: 'Curcumin nanoparticle potential inhibitory on glioblastoma cell line through down-regulation of epigenetic factors.' However, it should be noted that the original title was intended to emphasize the specific epigenetic factors involved, including HOTAIR, SUZ12, and DNMT3A. It is believed that this more specific title may better reflect the scope and findings of the study. Nevertheless, the title has been updated as per your request.

2- Why you select two method of nanoparticles preparation? "we used curcumin NPs produced through wet milling and ultrasonic methods." Which one was better? I didn't find the answer in abstract!

Answer: Thank you for your insightful comment. To clarify, in this study, curcumin nanoparticles were prepared exclusively using the ultrasonic method. The mention of wet milling was included as part of the literature context to provide background on alternative methods reported in previous studies. However, in our work, only the ultrasonic method was employed due to its ability to efficiently reduce particle size and ensure uniform dispersion. This method was chosen for its high reproducibility, simplicity, and suitability for preparing nanoparticles with the desired characteristics. We apologize for any confusion and will revise the manuscript to ensure the methodology is clearly described. Thank you for pointing this out.

3- "A transmission electron microscope (Zeiss-EM10C-80 KV, Germany) was used to investigate the morphology and size of curcumin NPs" this part should transfer to first part of "material and methods".

Answer: Thank you for the valuable suggestion. The statement regarding the use of the transmission electron microscope (Zeiss-EM10C-80 KV, Germany) has been moved to the first part of the 'Materials and Methods' section as requested.

4- "The results of the absorption spectrum measured with an ultraviolet-visible spectrometer were analyzed using Excel software. The highest NPs absorption was observed at the wavelength of 160 nm, and its value was equal to 0.51." Let me your conclusion clearly and the main purpose of UV analysis.

Answer: Thank you for your comment. The primary purpose of the UV-visible spectroscopy analysis was to confirm the successful synthesis of curcumin nanoparticles and to characterize

their optical properties. The absorption peak at 160 nm with a value of 0.51 indicates the presence of nanoparticles and their optical behavior. This result aligns with the expected range for curcumin nanoparticles, supporting the conclusion that the nanoparticles were successfully synthesized with the desired characteristics. The UV analysis also helped in understanding the light absorption behavior, which is critical for assessing the potential applications of the nanoparticles in biological systems. This information will be clarified in the revised manuscript.

5-Update your refrencess.

Answer: Thank you for your comment. The references in the manuscript have been carefully reviewed and updated to include the most recent and relevant studies. The revised version reflects these changes, ensuring that the citations are accurate, up-to-date, and aligned with the scope of the research.

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Revision (1)

Esmail Mohammadian : Reviewer

21 Dec 2024

Dear Editor

Have a nice day.

The author studied Curcumin nanoparticle has a potential inhibitory effect on glioblastoma cell line through down-regulation of epigenetic factors including HOTAIR, SUZ12 and DNMT3A.

It is recommended to be accepted for publication after the following minor changes.

1. Please mention quantitative results in the abstract section (with SD values).
2. The title needs to be changed.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reply to Reviewer Comments

Dear Referee,

Thank you for your valuable feedback and constructive suggestions on our manuscript. We appreciate your time and effort in reviewing our work. Below, we have addressed each of your comments in detail:

1. Please mention quantitative results in the abstract section (with SD values).

Answer: We have updated the abstract to include the quantitative results of our findings, along with standard deviation (SD) values, as per your suggestion. This addition ensures that the abstract provides a clear and precise summary of the study's outcomes.

2. The title needs to be changed.

Answer: The title has been revised to better reflect the study's content and objectives, as recommended. The updated title is:

" Down-Regulation of HOTAIR, SUZ12, and DNMT3A by Curcumin Nanoparticles in Glioblastoma."

We hope these revisions meet your expectations. Thank you again for your insightful comments and for considering our manuscript for publication.

Best regards,

OPEN PEER REVIEW

Revision (2)

Esmail Mohammadian : Reviewer

26 Jan 2025

Dear editor

Have a nice day.

The addressed issues and concerns have been effectively resolved. Consequently, the reviewer concurs to proceed with the publication of this paper in its current state.